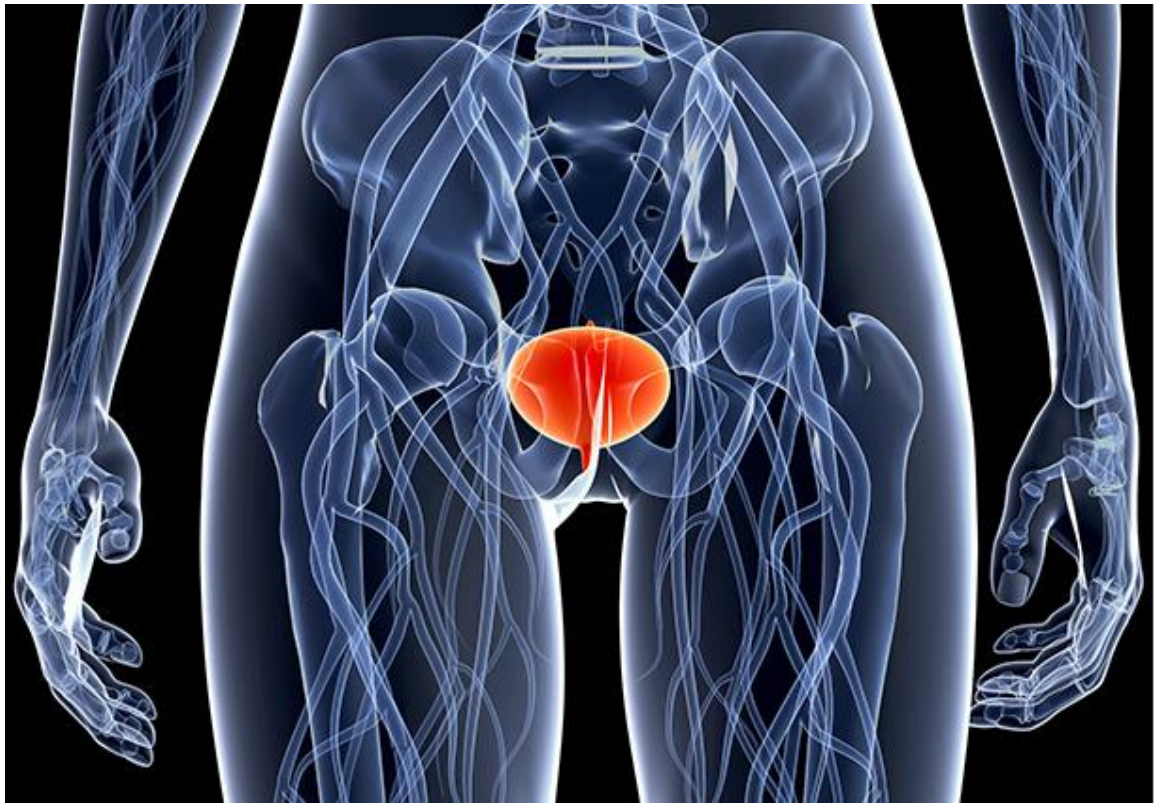
Evidence and Recommendations on Intravesical Treatments – when shortages occur



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THE TIMES

Drug shortage linked to bladder cancer deaths

Rosie Taylor

August 13 2019, 12:01am,
The Times

Health | Economics

SHORTAGE

...ge of Bacille Calmette-Guérin, an immunotherapy drug

...er of people surviving bladder cancer could be linked to a ...shortage of a key drug, experts have warned.

The proportion of bladder cancer patients in England living for at least five years after diagnosis has fallen from 55.1 per cent to 52.6 per cent, according to the Office for National Statistics. In the first statistically significant drop in survival rates in five years, the proportion of men surviving for five years or more with

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Health

A drop in the number of people surviving bladder cancer could be linked to a worldwide shortage of a key drug, experts have warned.

The proportion of bladder cancer patients in England living for at least five years after diagnosis has fallen from 55.1 per cent to 52.6 per cent, according to the Office for National Statistics. In the first statistically significant drop in survival rates in five years, the proportion of men surviving for five years or more with the disease fell from 58.6 per cent to 56.1 per cent.

Office for National Statistics. In the first statistically significant drop in survival rates in five years, the proportion of men surviving for five years or more with

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Drug shortage linked to bladder cancer deaths

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A drop in the number of people survi
worldwide shortage of

"In addition, the five-year survival rate for bladder cancer appears to be getting worse."

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from 55.1 per cent to 52.6 per cent, according to the
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rates in five years, the proportion of men surviving for five years or more with

BCG

- Transurethral resection of the bladder (TURBT)
- Non muscle invasive bladder cancer (NMIBC)
- Intermediate and High risk NMIBC (T1, high grade or carcinoma in situ) reduce recurrence / progression
- Challenging disease
- 80% recur / 45% progress – 5 years [1]
- EAU guidelines – BCG recommended in above pts and maintenance schedule 3 yrs HR, 1 yr intermediate risk [2]

[1] EAU Guidelines Eur Urol 2017;71: 447–61 ; [2] Babjuk M et al. Eur Urol. 2019; 76(5): 639-57

Risk stratification

Table 6.1: Weighting used to calculate disease recurrence and progression scores

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
≥ 8	6	3
Tumour diameter		
< 3 cm	0	0
≥ 3	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total Score	**0-17**	**0-23**

Table 6.2: Probability of recurrence and disease progression according to total score

Recurrence score	Probability of recurrence at 1 year		Probability of recurrence at 5 years	
	%	(95% CI)	%	(95% CI)
0	15	(10-19)	31	(24-37)
1-4	24	(21-26)	46	(42-49)
5-9	38	(35-41)	62	(58-65)
10-17	61	(55-67)	78	(73-84)

Progression score	Probability of progression at 1 year		Probability of progression at 5 years	
	%	(95% CI)	%	(95% CI)
0	0.2	(0-0.7)	0.8	(0-1.7)
2-6	1	(0.4-1.6)	6	(5-8)
7-13	5	(4-7)	17	(14-20)
14-23	17	(10-24)	45	(35-55)

BCG shortage

- 2011 Sanofi Pasteur's in Toronto
  - Connaught sub-strain live attenuated vaccine
  - TheraCyst and Immucyst
  - fungal colonisation – sterility issues
  - FDA shut down
- MERCK & Co. – TICE sub strain
  - Increase demand couldn't meet (estimated 2 million)
- 2012 Shortages started
- 2016 Sanofi Pasteur – to discontinue production
- Sustained worldwide shortage

Manufacturing

Merck limits orders for bladder cancer drug as demand outstrips supply

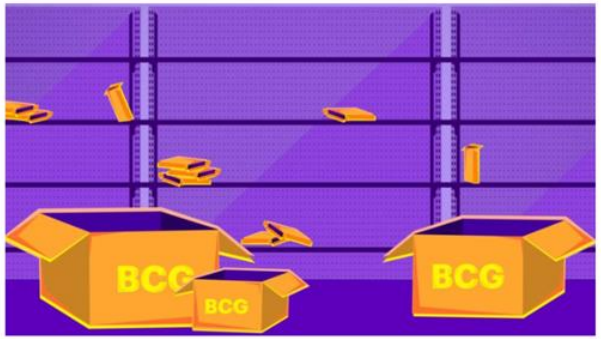
by Eric Sagonowsky | Mar 14, 2019 11:04am

Merck has been the sole supplier of bladder cancer drug BCG since 2012. (Merck)

HEALTH

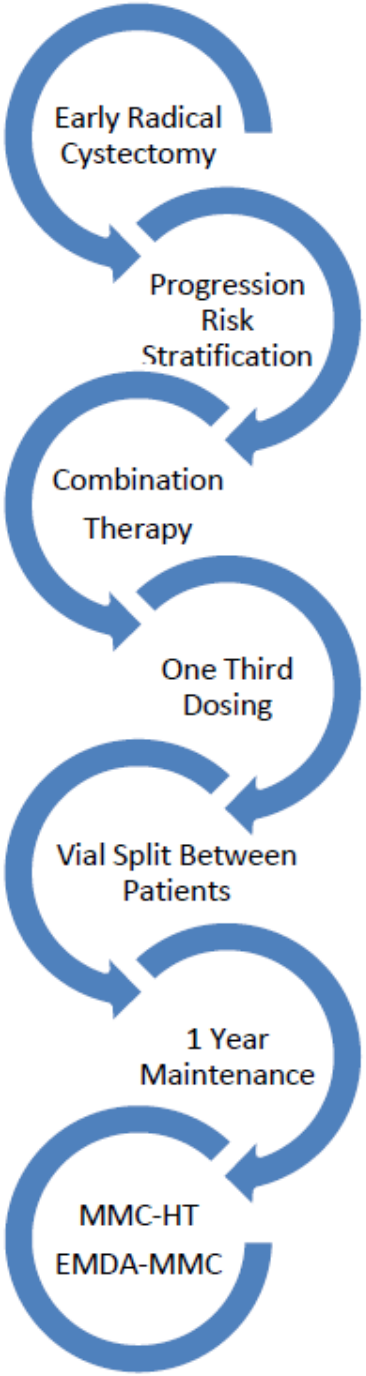
With one manufacturer and little money to be made, supplies of a critical cancer drug are dwindling

By MEGHANA KESHAVAN @megkesh / FEBRUARY 20, 2019



Various Implications …

- Use lower dose
- Less effective treatments
- Reducing maintenance courses / suboptimal treatment
- Newly diagnosed – Radical cystectomy
- Increase cost using other therapeutic options

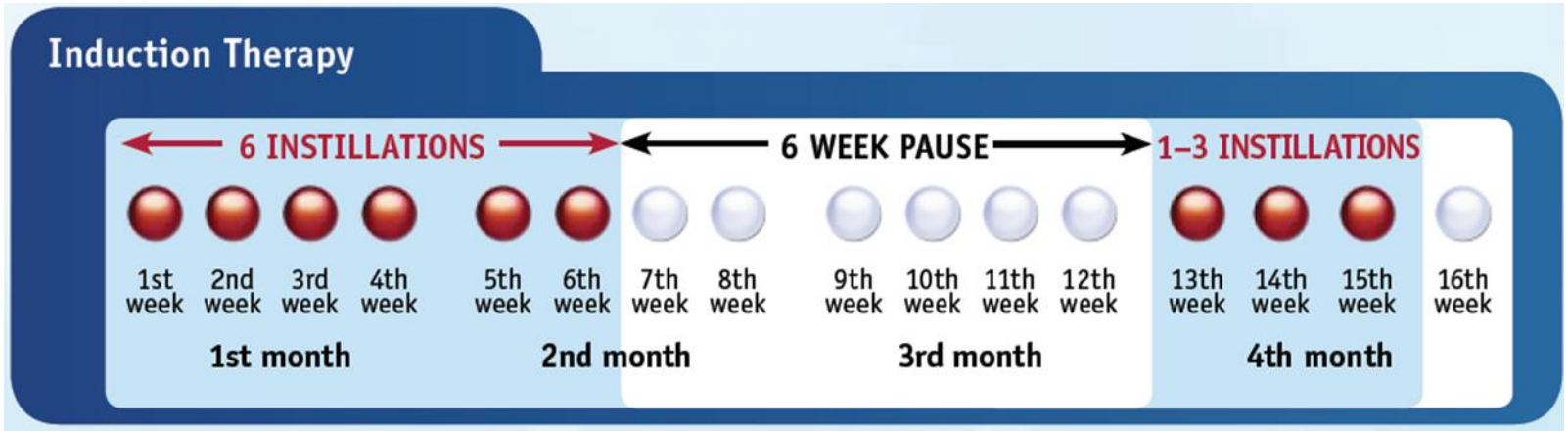


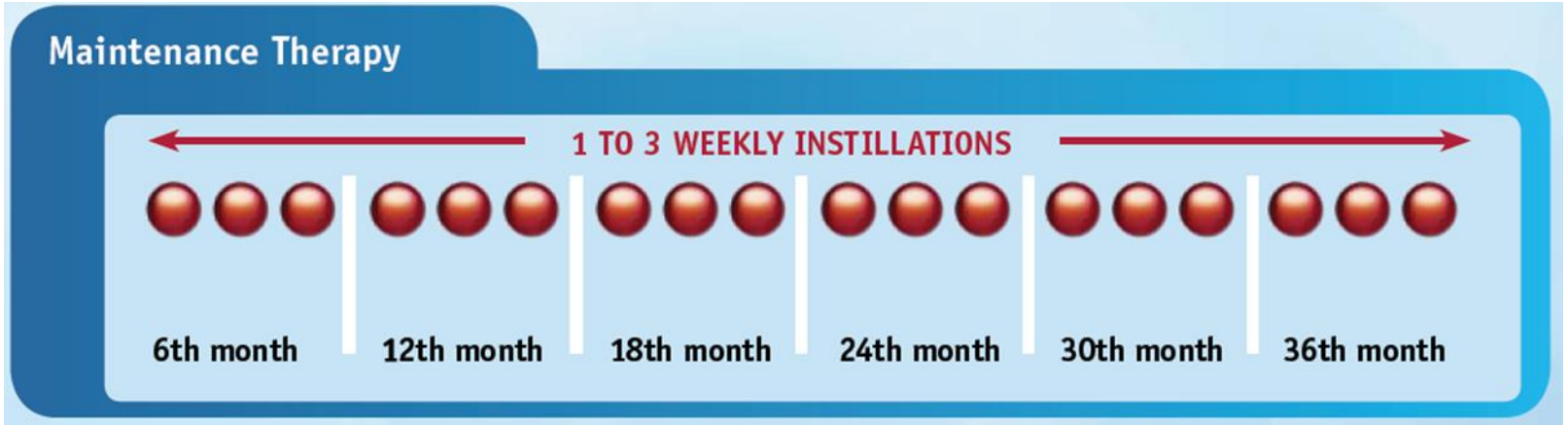
What does the literature say?

- Change of BCG schedule
- Change of BCG strain
- Intravesical chemotherapy
- Cystectomy

  - Reducing dose
  - Reducing BCG course
  - Reducing number of instillations per maintenance cycle

What is the optimal BCG schedule

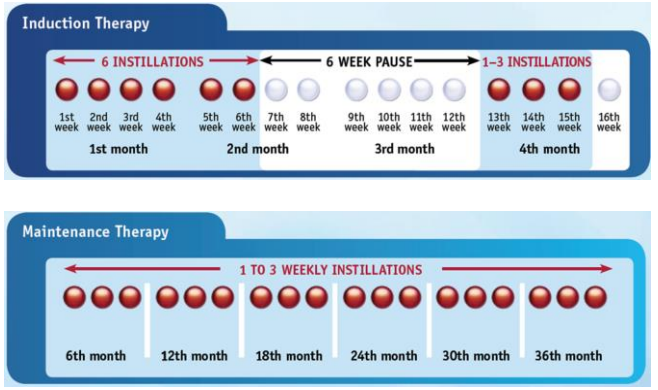




- 6 week induction
- 3 weekly maintenance
  - Reduce number

Lamm DL et al. J Urol 2000; 163: 1124-9

BCG schedule alternatives

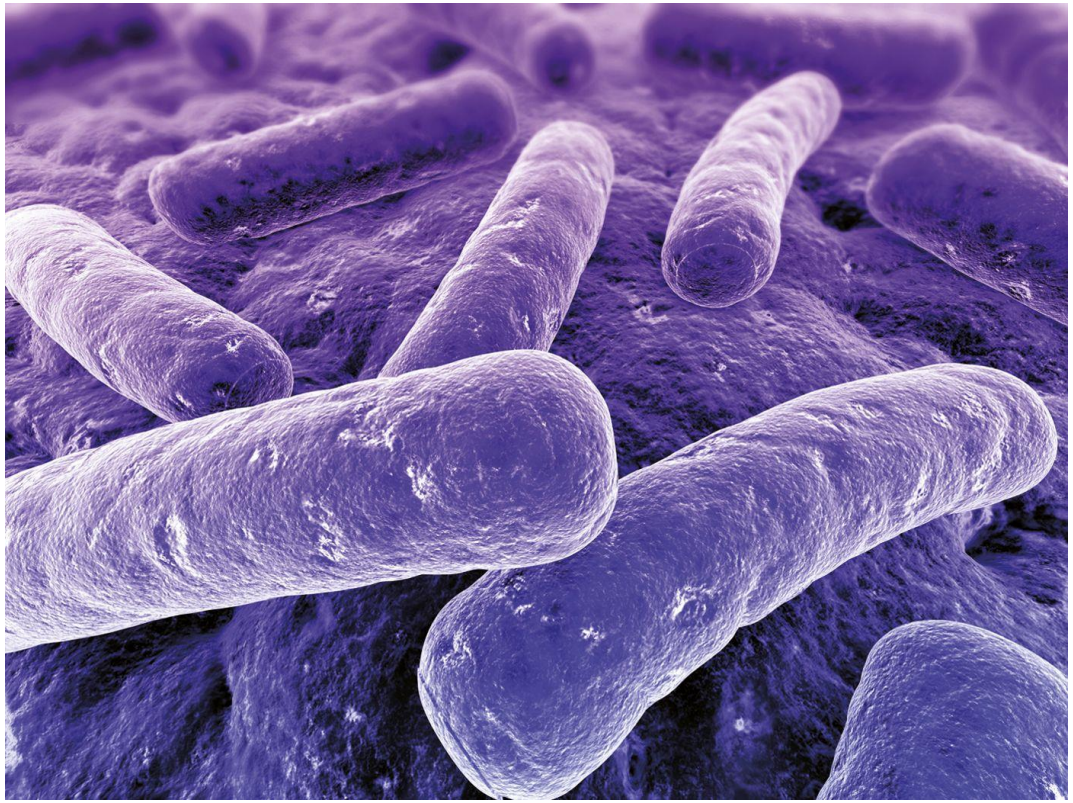


- 6 week induction
- 3 weekly maintenance
  - Reduce number
- EORTC-GU 3yrs full dose maintenance was not more efficient than 1yr full dose for intermediate risk [1]
- 1/3 full dose did not reduce recurrence (EAU do not recommend)
- Difficult reconstitution – closed system
- NIMBUS trial (NTR4011) – ongoing no. of maintenance

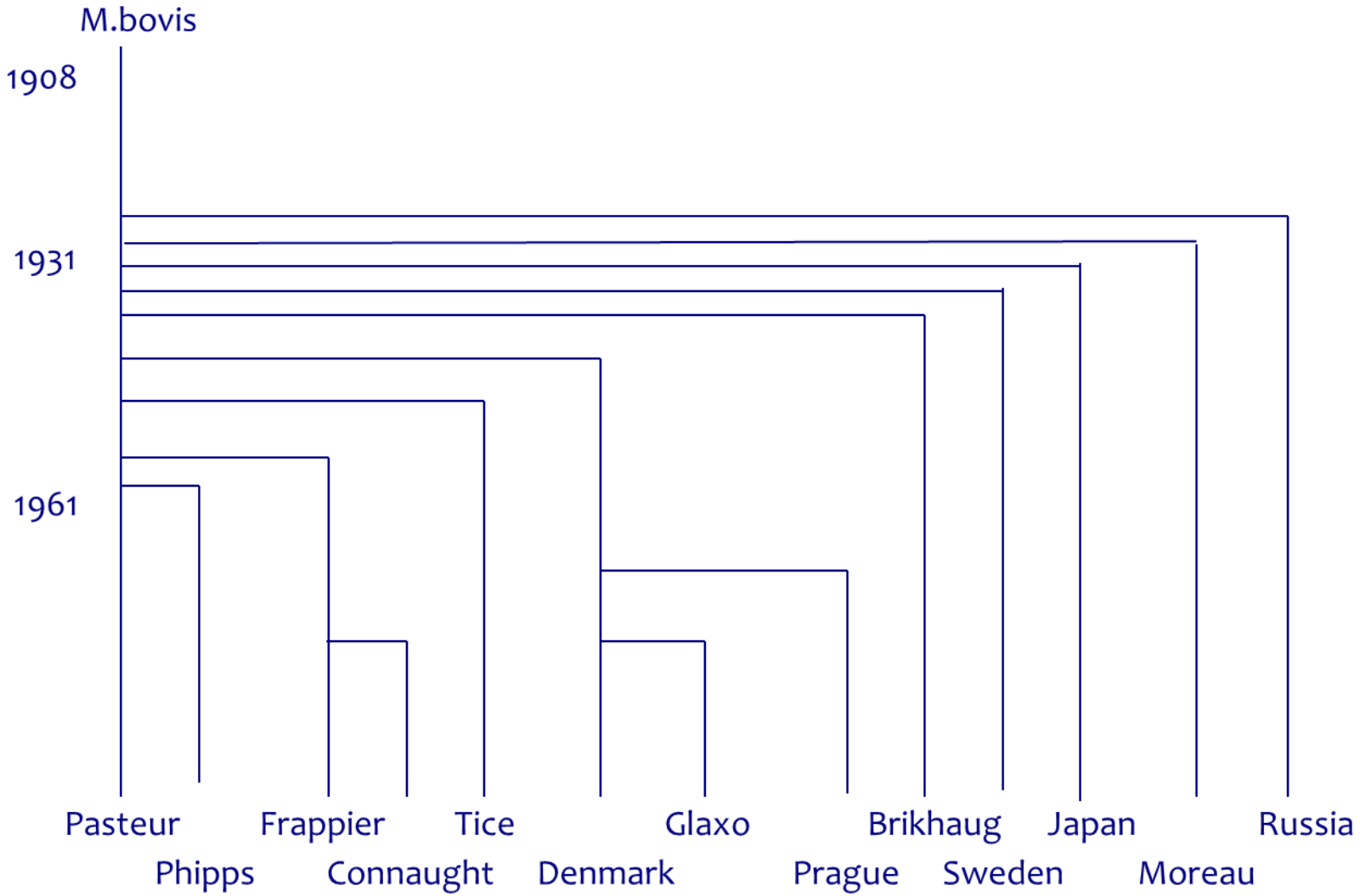
[1] *Oddens et al. Eur Urol 2013; 63: 462–72*

What does the literature say?

- Change of BCG schedule
- **Change of BCG strain**
- Intravesical chemotherapy
- Cystectomy



Availability of sub strains



Boehm BE et al. J Urol 2017; 198: 503–10.

BCG immunotherapy for bladder cancer- the effects of sub-strain differences

Strain	*n**	Mean CRR % (range)*	Commercial product	Weight (mg)	Recommended dose (cfu)‡	Secretion of lipid virulence factors?[61]	Secretion of MPB64/MPB70 and MPB83[76]
Moscow§	103	90.5	SII-ONCO-BCG® (Serum Institute, India)	120	$3–57\times10^8$	Yes	Present/High
Moreau RdJ	100	90	ImmunoBCG (FAP, Brazil)	80	0.04×10^8	No	Present/High
Connaught	450	79 (70–92)	Immunocyst® (Sanofi-Aventis, France)	81	$1.8–15.9\times10^8$	NT	NT
Tokyo	111	77 (63–84)	Tokyo 172 (QSMI, Thailand)	80	$0.4–0.5\times10^8$	No	Present/High
Pasteur	230	74 (40–80)	None	NA	NA	Yes	Absent/Present
Tice	277	71 (56–82)	OncoTice® (Merck, USA)	12.5	$2–8\times10^8$	Yes	Absent/Present
Glaxo	180	65 (53–88)	None	NA	NA	No	Absent/Present
A. Frappier	145	60 (39–100)	None	NA	NA	Yes	Absent/Present
S. African	13	69	None	NA	NA	NT	NT
Copenhagen	42	67	None	NA	NA	Yes	Absent/Present
Romanian	33	64	None	NA	NA	NT	NT
RIVM/1	15	60	BCG-Medac® (Medac, Germany)	80	$2–30\times10^8$	NT	NT

No meaningful correlations between BCG strain and survival outcomes (RFS, CSS, and OS)

Gan et al. Nat Rev Urol (2013)

Efficacy of bacillus Calmette-Guérin Strains for Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Network Meta-Analysis

Brock E. Boehm, John E. Cornell, Hanzhang Wang, Neelam Mukherjee, Jacob S. Oppenheimer and Robert S. Svatek*

Department of Urology and Department of Biostatistics (JEC), University of Texas Health San Antonio, San Antonio, Texas

Purpose: We sought to determine the efficacy of genetically distinct bacillus Calmette-Guérin strains in preventing disease recurrence in patients with nonmuscle invasive bladder cancer.

Materials and Methods: We conducted a systematic review and network meta-analysis of trials evaluating bacillus Calmette-Guérin strains against all possible comparators (different bacillus Calmette-Guérin strains, chemotherapy and nonbacillus Calmette-Guérin biological therapies) with intravesical chemotherapy as the common comparator. MEDLINE® (http://www.ncbi.nlm.nih.gov/pubmed) served as the primary data source, with the search from inception to October 2016 for clinical trials involving patients with nonmuscle invasive bladder cancer receiving bacillus Calmette-Guérin. Primary outcome measure was bladder cancer recurrence, defined as recurrent bladder tumor of any grade or stage. Random effect network meta-analysis provided estimates for outcomes and is presented as odds ratios.

Results: Across all possible comparators (65 trials, 12,246 patients, 9 strains) there were 2,177 recurrences in 5,642 treated patients (38.6%) and 2,316 recurrences in 5,441 comparators (42.6%). With chemotherapy as the common comparator (28 trials, 5,757 patients, 5 strains) Tokyo-172 (OR 0.39, 95% CI 0.16–0.93), Pasteur (OR 0.49, 95% CI 0.28–0.86) and TICE® (OR 0.61, 95% CI 0.40–0.93) strains were significantly better than chemotherapy at preventing recurrence. No bacillus Calmette-Guérin strain demonstrated significant superiority when compared to any other strain at preventing recurrence in the network meta-analysis.

Conclusions: Bacillus Calmette-Guérin strains exhibited significant differences in efficacy compared to chemotherapy. However, no definitive conclusions could be reached regarding strain superiority, and head-to-head trials are greatly needed to further understand the importance of strain selection in determining bacillus Calmette-Guérin efficacy.

Abbrev
and Ac
BCG = b
CIS = ca
FDA = U
Drug Adr
MeSH =
Headings
NMIBC =
bladder c
PRISMA
Items for
Meta-An
RIVM =
Institute
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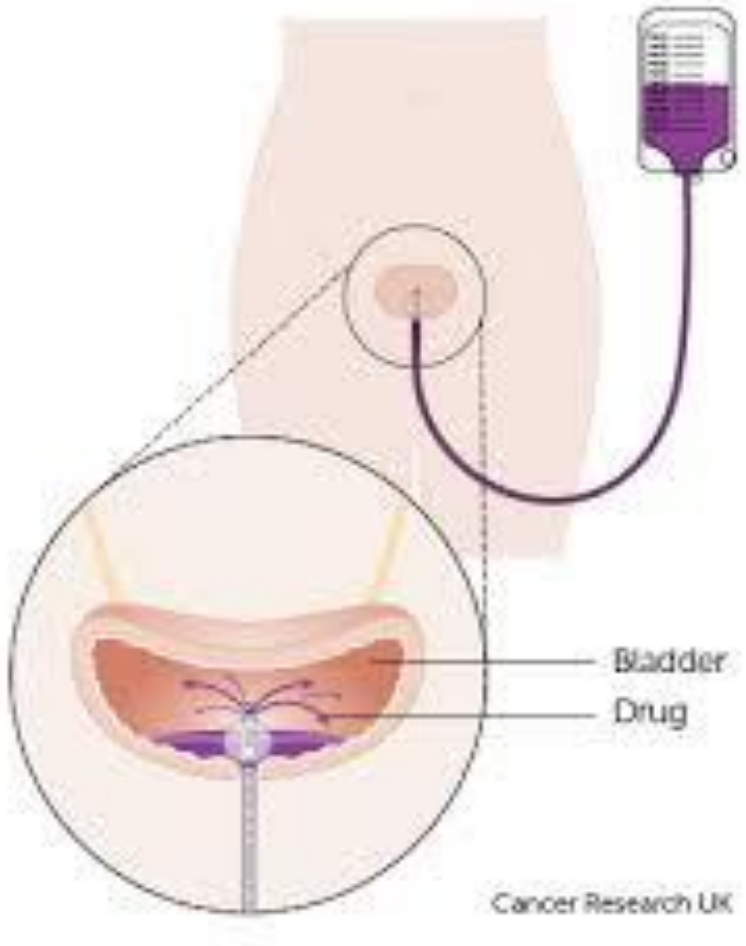
Boehm et al. J Urol 2017; 198: 503-10.

What does the literature say?

- Change of BCG schedule
- Change of BCG strain
- Intravesical chemotherapy
- Cystectomy



EUROPEAN UROLOGY 56 (2009) 247–256

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Bladder Cancer

Editorial by Guido Dalbagni on pp. 257–258 of this issue

An Individual Patient Data Meta-Analysis of the Long-Term Outcome of Randomised Studies Comparing Intravesical Mitomycin C versus Bacillus Calmette-Guérin for Non–Muscle-Invasive Bladder Cancer

Per-Uno Malmström[a,], Richard J. Sylvester[b], David E. Crawford[c], Martin Friedrich[d], Susanne Krege[e], Erkki Rintala[f], Eduardo Solsona[g], Savino M. Di Stasi[h], J. Alfred Witjes[i]*

Malmstrom et al. Eur Urol 2009;56: 247-56

Alternative adjuvant intravesical therapies

- Mitomycin C (MMC) with 1 year maintenance (optimal not clear)
- Higher risk of recurrence
- Lower HR patients – G3pTa no CIS (pT1 or CIS – alternative)
- Malstrom [1] – did not find a statistically significant difference between BCG or MMC in terms of progression, cancer specific or overall survival
- Fewer side effects than BCG

[1] *Malmstrom et al. Eur Urol 2009;56: 247-56*

EUROPEAN UROLOGY 56 (2009) 247–256

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Bladder Cancer

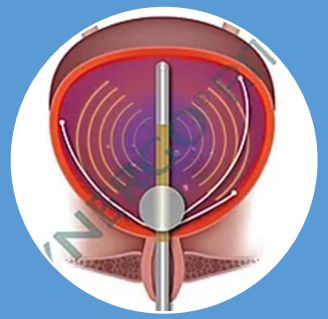
Editorial by Guido Dalbagni on pp. 257–258 of this issue

Conclusions: For prophylaxis of recurrence, maintenance BCG is required to demonstrate superiority to MMC. Prior intravesical chemotherapy was not a confounder. There were no statistically significant differences regarding progression, overall survival, and cancer-specific survival between the two treatments.

Per-Uno Malmström[a,], Richard J. Sylvester[b], David E. Crawford[c], Martin Friedrich[d]*
Susanne Krege[e], Erkki Rintala[f], Eduardo Solsona[g], Savino M. Di Stasi[h], J. Alfred Witjes[i]

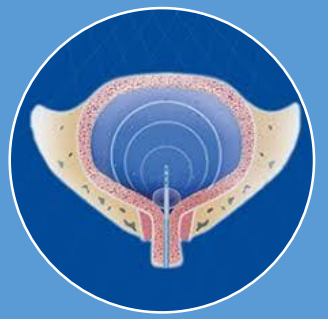
Malmstrom et al. Eur Urol 2009;56: 247-56

Devices to enhance intravesical chemotherapy



Radiofrequency-induced thermochemotherapeutic effect (RITE), hyperthermic

conductive chemotherapy

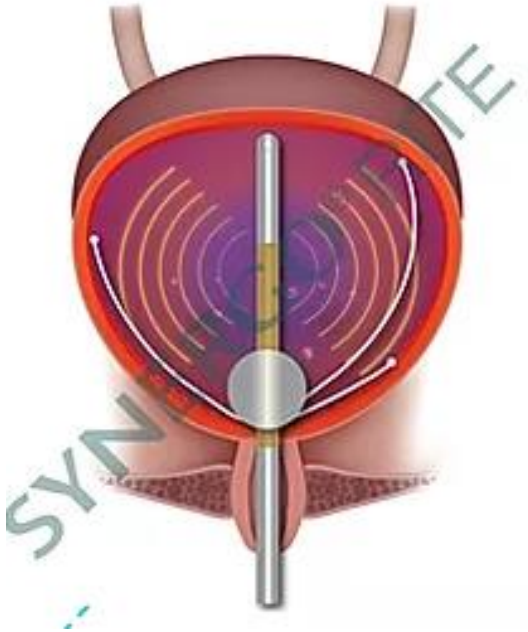


electromotive drug administration (EMDA)

Tan WS, Kelly JD Nature Rev Urol. 2018: 15(11): 667-85

Device-assisted intravesical chemotherapy

- Thermochemotherapy (TC) – Hyperthermia and MMC (Synergo)
  - Long term data on patients with intermediate and HR NMIBC – low rates of recurrence in comparison MMC alone [1]
- Arends et al – RCT showed TC reliable alternative [2]
- No data on effect of treatment modality on disease progression
  - Attractive option though for HG disease when no BCG and no RC



[1] *Arends TJH et al. Eur Urol 2016; 69: 1046–52 ;* [2] *Colombo R et al. BJU Int 2011; 107: 912- 8.*

Chemohyperthermia - Combat

- Patients with CIS had a lower disease-free survival with chemohyperthermia.
- The HIVEC 1&2 trials investigating the use of conductive chemohyperthermia are currently under way [1]

[1] *Dan et al. Eur Urol Supps 2017; 16(3): 1150*

EUROPEAN UROLOGY 69 (2016) 1046–1052

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Bladder Cancer

Editorial by Jorg R. Oddens and Richard J. Sylvester on pp. 1053–1054 of this issue

Results of a Randomised Controlled Trial Comparing Intravesical Chemohyperthermia with Mitomycin C Versus Bacillus Calmette-Guérin for Adjuvant Treatment of Patients with Intermediate- and High-risk Non–Muscle-invasive Bladder Cancer

Tom J.H. Arends [a], Ofer Nativ [b], Massimo Maffezzini [c], Ottavio de Cobelli [d], Giorgio Canepa [c], Fabrizio Verweij [e], Boaz Moskovitz [b], Antoine G. van der Heijden [a], J. Alfred Witjes [a,]*

[a] *Radboud University Medical Centre, Nijmegen, The Netherlands;* [b] *Bnai-Zion Hospital, Haifa, Israel;* [c] *Ente Ospedaliero Ospedali Galliera, Genova, Italy;* [d] *Istituto Europeo di Oncologia, Milan, Italy;* [e] *IRCCS Multimedica, Milan, Italy*

[1] *Arends TJH et al. Eur Urol 2016; 69: 1046–52*

EUROPEAN UROLOGY 69 (2016) 1046–1052

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

5. Conclusions

CHT is a safe and effective treatment option in patients with intermediate- and high-risk papillary NMIBC. These data suggest that CHT therapy is more effective than BCG therapy. According to the results above and the recent worldwide shortages of BCG, urologists might consider CHT as an option instead of BCG therapy as adjuvant treatment for papillary intermediate- and high-risk NMIBC.

Tom J.H. Arends[a], Ofer Nativ[c], Massimo Maffezzini[c], Ottavio de Cobelli[d], Giorgio Canepa[c], Fabrizio Verweij[e], Boaz Moskovitz[b], Antoine G. van der Heijden[a], J. Alfred Witjes[a,]*

[a] *Radboud University Medical Centre, Nijmegen, The Netherlands;* [b] *Bnai-Zion Hospital, Haifa, Israel;* [c] *Ente Ospedaliero Ospedali Galliera, Genova, Italy;* [d] *Istituto Europeo di Oncologia, Milan, Italy;* [e] *IRCCS Multimedica, Milan, Italy*

[1] *Arends TJH et al. Eur Urol 2016; 69: 1046–52*

EMDA intravesical chemotherapy

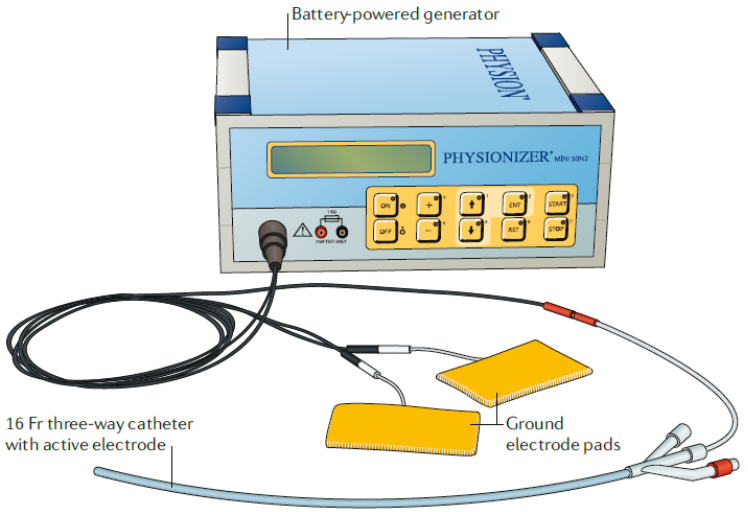
- Electromotive device assisted (EMDA)
- Di Stasi – RCT lower rec and progression [1]
- Cochrane database systemic review assessed effect of EMDA MMC – concluding maybe delay in rec. and potential role when other agents not available [2]

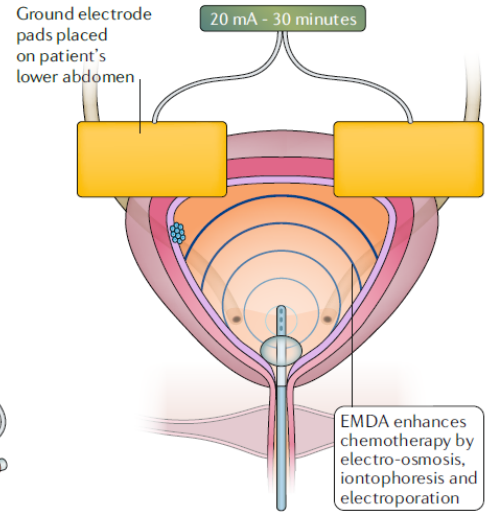
lower recurrence (42% vs 58%),

progression (9% vs 22%,

disease-specific (6% vs 16%)

overall mortality (22% vs 32%)





[1] *Di Stasi SM et al. Lancet Oncol 2006; 7: 43–51 ;*

[2] *Jung JH et al. Cochrane Database Syst Rev 2017; 9: CD011864*

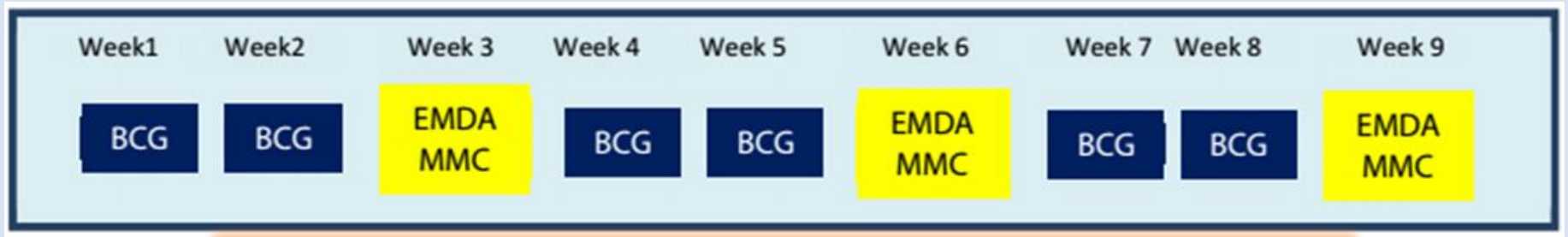
The Journal of Urology. 195(6):1697–1703, JUN 2016
DOI: 10.1016/j.juro.2016.01.103, PMID: 26845426
Issn Print: 0022-5347
Publication Date: 2016/06/01

Print

Sequential bacillus Calmette-Guérin/Electromotive Drug Administration of Mitomycin C as the Standard Intravesical Regimen in High Risk Nonmuscle Invasive Bladder Cancer: 2-Year Outcomes

Christine Gan;Suzanne Amery;Kathryn Chatterton;Muhammad Khan;Kay Thomas;Tim O'Brien;

+ Author Information



- Progression rates reduced (9% v 21%)
- Mortality reduced (21% v 32%)

Conclusions:

This study confirms the excellent oncologic efficacy of sequential bacillus Calmette-Guérin/electromotive drug administration of mitomycin C in cases of high risk, nonmuscle invasive bladder cancer. Tolerability is a challenge but alterations to the 9-week schedule appeared to have a negligible impact on outcomes.

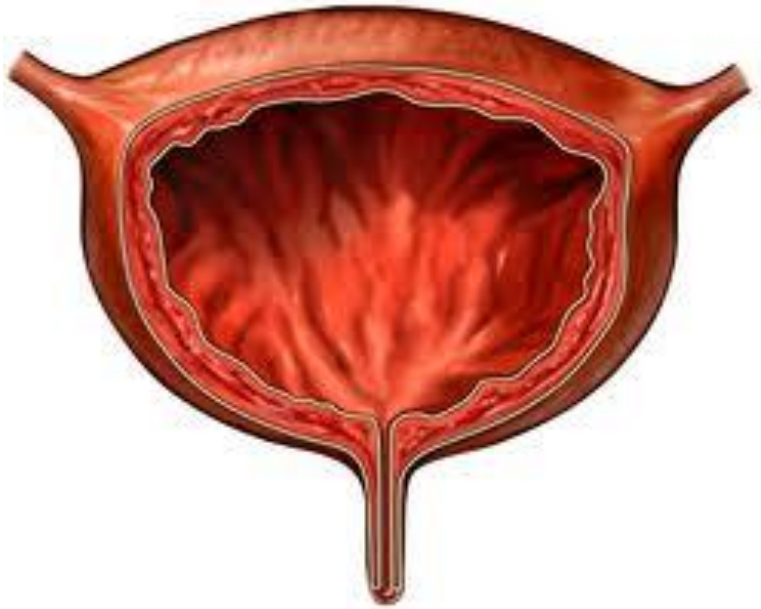
Gan et al. J Urol 2016; 195(6): 1697- 1703

Intravesical gemcitabine

Similar efficacy to BCG in intermediate risk NMIBC[1]

Higher efficacy in BCG-refractory patients with lower toxicity profile[2]

No phase III trials gemcitabine vs BCG



[1] *Shelley MD et al. BJU Int 2012; 109: 496- 505;* [2]*Addeo R et al. J Clin Oncol 2010; 28: 543– 8.*

2 randomised trials comparing between gemcitabine and BCG in BCG-niave NMIBC

Primary Ta / T1 disease without CIS were randomised to receive 6/52 intravesical instillations of either gemcitabine or BCG. There were no significant differences in the recurrence and progression rates between the two groups. [1]

Patients with HR NMIBC were randomised to receive three years of either gemcitabine or BCG. Patients in the gemcitabine group had a higher recurrence rate than the BCG group (53% vs 28%). [2]

None of the patients developed disease progression

[1] *Bendary L et al. J Urol. 2011; 185(4S): e664-e5 ;* [2] *Porena M et al. Urol Int. 2010; 84(1): 23-7.*

Epirubicin

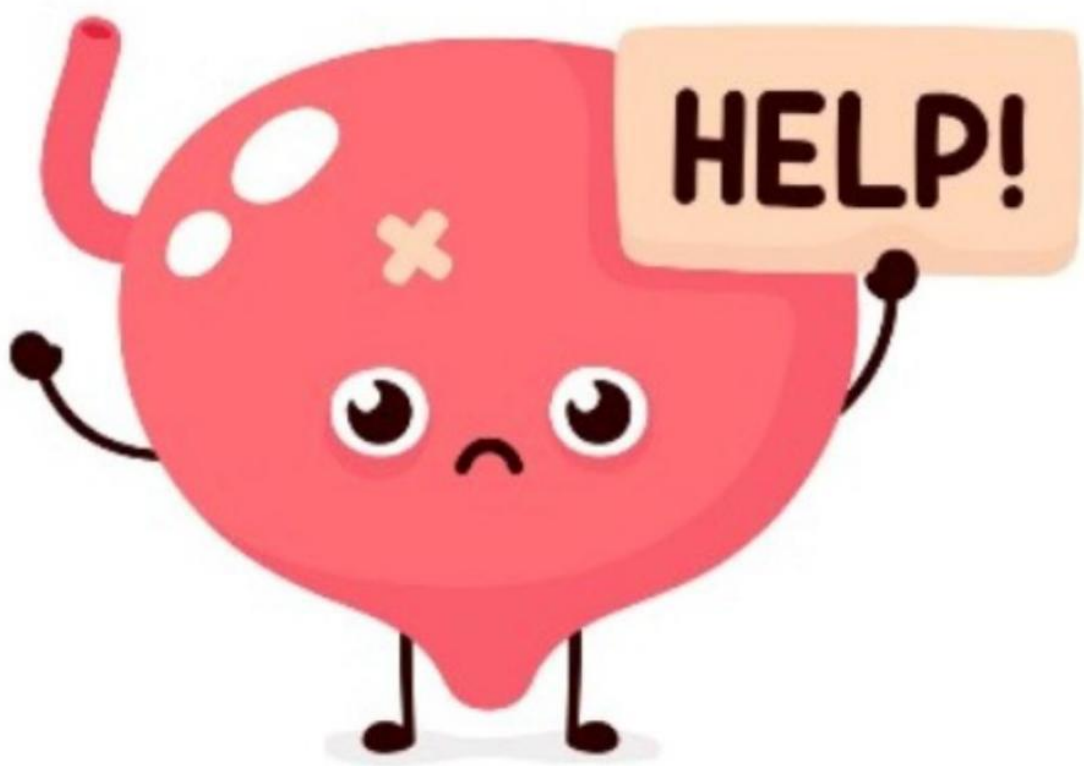
- Two randomised trials compared epirubicin with BCG showing inferior oncological outcomes with epirubicin
- Intermediate- and HR NMIBC patients up to 3yrs BCG had lower risks of recurrence, distant metastasis, bladder cancer-specific mortality and overall mortality than those who received up to three years of intravesical epirubicin [1]
- In a second trial comparing BCG with the combination of epirubicin and interferon-α2b, a better disease-free survival was observed in the BCG group [2]

- **Lack of evidence**
- **Need RTs**
- **With progression as primary endpoint**

[1] *Sylvester RJ et al. Eur Urol. 2010; 57(5): 766-3* [2] *Duchek M et al. Eur Urol. 2010; 57(1): 25-31.*

What does the literature say?

- Change of BCG schedule
- Change of BCG strain
- Intravesical chemotherapy
- Cystectomy



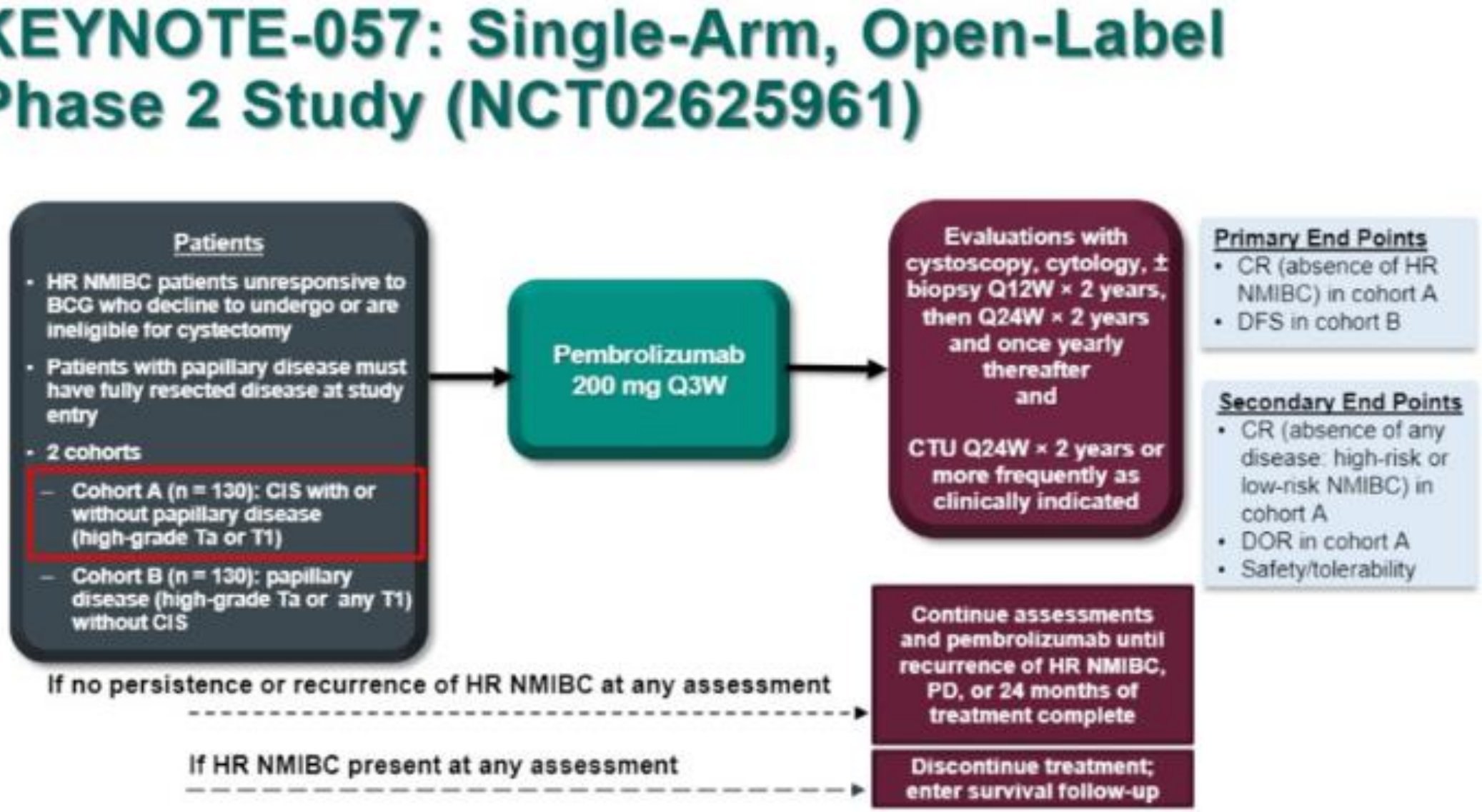
Radical cystectomy

- Despite treatment (TUR and BCG) 20% will progress to MIBC
  - the progression rate can be up to 17% at one-year and 45% at 5 years [1]
- WE don't want to over treat patients i.e. if respond to BCG
- BUT HR disease progression i.e. LVI and variant histology consider RC even if BCG present[2]

- 50% will be over treated with primary cystectomy [3]
  - Careful selection, benefits and risks / excellent oncological outcome

[1] Sylvester RJ et al. Eur Orol. 2006; 49(3(: 46-5. discussion 75-7. [2] D'Andrea D et al. Urol Oncol Semin Orig Investig 2018; 36: 239. [3] EAU Guidelines Eur Urol 2017;71: 447–61

Is BCG as good as immunotherapy??!



KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)

Overall Response Rate at Month 3[a]

Response	Total Population (N = 102)		
	n	%	95% CI
CR	**41**	**40.2**	**30.6-50.4**
Non-CR	57	55.9	45.7-65.7
Persistent[b]	41	40.2	30.6-50.4
Recurrent[c]	6	5.9	2.2-12.4
NMIBC stage progression[d]	9	8.8	4.1-16.1
Non-bladder malignancy[e]	1	1.0	0.0-5.3
Progression to T2	0	0	NA-NA
Nonevaluable[f]	4	3.9	1.1-9.7

Conclusions

- BCG shortage is a health-threatening problem
- Initial TURBT paramount
- No superiority of one BCG sub-strain over the other
- One-year intravesical mitomycin C is an alternative treatment option in intermediate risk
- BCG Maintenance therapy can be stopped after 1 year in HR patients

Conclusions

- Chemohyperthermia and electromotive usage of MMC may represent an alternative to BCG
- Intravesical thermochemotherapy with MMC can be offered with CIS / pT1 when BCG not available and radical cystectomy is not feasible
- Intravesical chemotherapies such as Gemcitabine and Epirubicin should be used when both BCG and MMC are in short supply
- Upfront cystectomy should be discussed with high-risk NMIBC patients in severe BCG shortage


BONUS

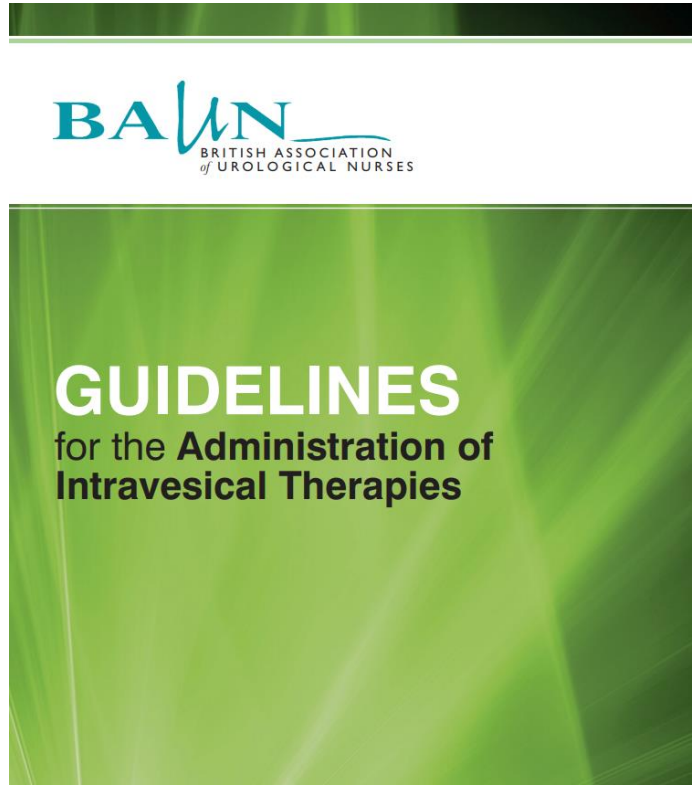
Mitomycin

Intravesical administration of mitomycin is recommended by NICE in the following patient groups [1]

- Patients with suspected bladder cancer after trans-urethral resection of bladder tumour (TURBT)
- Newly diagnosed intermediate risk bladder cancer. As a weekly dosing schedule for 6 courses

[1] *Bladder cancer: diagnosis and management. NICE guideline [NG2] Published date: February 2015.*

- Kyowa Kirin 80% of market for bladder
- October 2019 – sterility issues
- MEDAC – current customers
- Accord – not actively held in this country



- Intravesical chemotherapies such as Gemcitabine and Epirubicin should be used when both BCG and MMC are in short supply.

Local management options

- Intravesical gemcitabine (2g in 100ml) or Epirubicin (50mg in 50-100ml) Post TURBT
- Treatment courses of gemcitabine (2g in 100ml) or Epirubicin
- Must be available in ready-to-administer urotainers – chemo pharmacy
- Ensure all high-risk patients receive treatment courses with BCG rather than mitomycin-C as per NICE Guidance.
- Non-mitomycin-C containing cytotoxic chemo-radiotherapy regimens are used to treat locally advanced or muscle invasive bladder cancer in line with NICE Guidance.

NHS Specialist Pharmacy Service UKMi UK Medicines Information

Memo (for local adaptation) - shortage of supply

NICE guideline [NG2] Published date: February 2015.

Be in control! ☺

- Work closely with pharmacy / Control of stock levels
- Weekly meetings
- Weekly clinic discussions – additions
- Prioritise patients on a case by case basis
- Individualised care
- Attempt completion of courses
- Face to face explanations

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